OIPE IAP86
DEC 10 2007
PATENT & TRADEMARK OFFICE

Office Action Summary	**Application No.**	**Applicant(s)**	
	10/684,249	NGUYEN ET AL.	
	Examiner	**Art Unit**	
	Amber D. Steele	1639	

*-- The **MAILING DATE** of this communication appears on the cover sheet with the correspondence address --*

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2007*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-37* is/are pending in the application.
4a) Of the above claim(s) *34-36* is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *24-33 and 37* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *10/13/03*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-18 were originally filed on October 13, 2003.

A duplicate of the original claims was filed on March 4, 2004.

A triplicate of the original claims was filed on October 13, 2006.

The amendment to the claims received on November 30, 2006 canceled claims 10-13 and 15-18 and added new claims 19-23.

The amendment to the claims received on February 23, 2007 provided improper status identifiers for claims 10-13 and 15-21 and amended claims 22-23.

The amendment to the claims received on June 4, 2007 amended claim 1 and canceled claims 10-13 and 15-23.

The amendment to the claims received on July 16, 2007 canceled claims 1-23 and added new claims 24-37.

Two additional claim amendments were received by the Office, but were not entered.

Claims 24-37 are currently pending.

Claims 24-33 and 37 are currently under consideration.

2. Applicants are respectfully requested to only submit claim sets, specification, abstract, etc. when amendments are being made. It is not necessary to submit claims, specification, abstract, etc. with each response if amendments are not being made.

Pro Se

3. An examination of this application reveals that applicant is unfamiliar with patent prosecution procedure. While an inventor may prosecute the application, lack of skill in this field usually acts as a liability in affording the maximum protection for the invention disclosed. Applicant is advised to secure the services of a registered patent attorney or agent to prosecute the application, since the value of a patent is largely dependent upon skilled preparation and prosecution. The Office cannot aid in selecting an attorney or agent.

A listing of registered patent attorneys and agents is available on the USPTO Internet web site http://www.uspto.gov in the Site Index under "Attorney and Agent Roster." Applicants may also obtain a list of registered patent attorneys and agents located in their area by writing to the Mail Stop OED, Director of the U. S. Patent and Trademark Office, PO Box 1450, Alexandria, VA 22313-1450

Election/Restrictions

4. Applicant's election of amine as the species of compound in the reply filed on July 16, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

5. Please note: applicants elected specific compounds (i.e. 3-phenyl-1-propylamine and derivatives) that were not disclosed in the specification as originally filed. These compounds would be considered new matter if attempts are made to incorporate the specific compounds into the specification or claims. Please refer to MPEP § 2163.06.

6. Claims 34-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 16, 2007.

Priority

7. No priority is claimed.

Information Disclosure Statement

8. The information disclosure statement (IDS) submitted on October 13, 2003 is being considered by the examiner.

Drawings

9. The subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention. Applicant is required to furnish a drawing under 37 CFR 1.81(c). No new matter may be introduced in the required drawing. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d).

Abstract

10. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

11. The abstract of the disclosure is objected to because the abstract contains legal phraseology (i.e. "said"). Correction is required. See MPEP § 608.01(b).

Invention as Claimed

12. An automated method of determination of metabolic stability of library of compounds from cytochrome P450 enzyme reactions by isotope dilution mass spectrometric analysis comprising the steps of:

a) converting a portion of each said library compound into a stable isotope labeled internal standard by addition of a stable isotope labeled chemical reagent;

b) converting another portion of each said library compound into a compound of identical structure, with the exception of the stable isotope atoms, as that of said stable isotope labeled internal standard comprising addition of a non- isotope version of said stable isotope reagent;

c)-separating said stable isotope labeled internal standards and said non- isotope labeled converted compounds by an extraction method;

d) incubating other portions of said library of compounds in the presence of cytochrome P450 enzyme systems at body temperature for periods of time;

e) adding quenching chemical reagents to terminate said enzyme reactions;

f) adding said stable isotope labeled internal standards to said terminated reactions;

g) adding said non-isotope version of said stable isotope labeled chemical reagent to said terminated reactions to convert the remaining of each said library compound into said non-isotope labeled converted compounds;

h) separating said converted compound and its internal standard from said reactions by an extraction method;

i) determining the molecular ions of said stable isotope labeled internal standards and said non-isotope labeled converted compounds;

j) determining the most abundant daughter ions of said stable isotope labeled internal standards and said non-isotope labeled converted compounds;

k) determining the ion ratio of said converted compound to said corresponding internal standard for each of said enzyme reactions using tandem mode of mass spectrometric analysis; and

l) determining the percent remaining of each said library compound from said enzyme reactions from said ion ratios and variations thereof.

Claim Objections

13. Claims 24-33 and 37 are objected to because of the following informalities:

An alternative preamble for claim 24 is suggested: "An automated method for determining metabolic stability of a library of compounds…".

An alternative to method step h is suggested "…and the stable isotope labeled internal standard which corresponds to a compound of the library".

In addition, library of compounds may be utilized when referring to more than one compound and compound may be utilized when referring to a single member of the library (please refer to claim 24 method steps a, d, g, l; claims 27, 33).

Claim 33 recites a Markush group. However, the proper format for a Markush claim is not utilized. Please refer to MPEP § 803.02 which states that a Markush-type claim recites alternatives in a format such as "selected from the group consisting of A, B

and C." See Ex parte Markush, 1925 C.D. 126 (Comm'r Pat. 1925). Applicants have written alternative language in the Markush group and not in the accepted form (i.e. "selected from a labeled acid anhydride **or** labeled acid chloride....**and** labeled thiosocyanate").

The spacing of the lines of the claims is such as to make reading difficult. New application papers with lines 1½ or double spaced on good quality paper are required. 37 CFR 1.52 (b) (2) (i); MPEP 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 24-33 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

Claim 24 is drawn to a method for determining the metabolic stability of a library of compounds comprising (a) producing a stable isotope labeled internal standard via addition of a chemical reagent to a compound, (b) producing compounds that are identical in structure to the internal standards except for the stable isotope atoms, (c) separating the standards and compounds, (d) incubating compounds with cytochrome P450 enzyme systems, (e) adding quenching chemical reagents to terminate reactions, (f) adding internal standards, (g) adding non-isotope labeled chemical reagents, (h) separating compounds form internal standards, (i) determining molecular ions, (j) determining most abundant daughter ions, (k) determining ion rations, and (l) determining the percent remaining of each compound. The invention as claimed requires compounds, internal standards that correlate to the compounds, various chemical reagents including isotope labeled, non-isotope labeled, quenching, etc., and a member of the cytochrome P450 superfamily. The claimed invention does not include any structural information (i.e. actual structure or names of art-recognized species) regarding the compounds, internal standards, or chemical reagents except that the compound and internal standard must be identical in structure except for the stable isotope atoms of the internal standard. Therefore, the claimed invention includes all compounds, all internal standards with stable isotopes, and all chemical reagents without providing information regarding how the chemical reagents alter the structure of the compounds and internal standards.

The specification teaches a single example utilizing amines (i.e. amine 1, amine 2, amine 3, and amine 4) as compounds, acetamide-d3 internal standards, and chemical reagents including acetic anhydride-d6 (for producing internal standards), acetonitrile (terminating reagent), sodium bicarbonate and acetic anhydride (for conversion). In addition, applicants also lists various generic compounds (i.e. drug compounds, amines, alcohols, aldehydes, and carboxylic acids), generic stable internal standards (i.e. drug compounds, amines, alcohols, aldehydes, and carboxylic acids with stable isotopes), the generic cytochrome P450 superfamily, and various chemical reagents (i.e. acid anhydride, acid chloride, chloroformate, isocyanate, thioisocyanate) without adequately describing how to utilize the various reagents in combination in the method as presently claimed or providing specific species of any of the claimed genera (i.e. compound, cytochrome P450 enzyme superfamily, etc.). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species). Therefore, one skilled in the relevant art would not reasonably conclude that the applicants had possession of the invention as claimed.

See Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

17. Claims 24-33 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 recites the limitation "said stable isotope reagent" in line 4 of method step b. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "said non-isotope labeled converted compounds" in lines 1-2 of method step c, line 3 of method step g, line 2 of method step I, line 2 of method step j. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "said terminated reactions" in lines 1-2 of method step f and in line 2 of method step g. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "said converted compound" in line 1 of method step h and line 1 of methods step k. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "said reactions" in lines 1-2 of method step h. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "said corresponding internal standard" in lines 1-2 of method step k. There is insufficient antecedent basis for this limitation in the claim.

Claim 27 recites the limitation "said sample" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the limitation "said internal standard" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 29 recites the limitation "said internal standard" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

Claim 29 recites the limitation "said chemical reagent" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

Claim 33 recites the limitation "said stable isotope reagent" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 33 recites the limitation "said resulting internal standards" in lines 4-5. There is insufficient antecedent basis for this limitation in the claim.

18. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention. The claims and the specification do not define the classes of library compounds. For example, does a class comprise a single compound, compounds that are structurally related, compounds that are functionally related, etc.?

19. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention. The claims and the specification do not define a 100% quantitative conversion. For example, is a 100% quantitative conversion a reaction wherein 100% of the reactants have formed a product, what are the parameters for quantification (i.e. mass, amount of final product, analysis of reactants, analysis of rate limiting reactant, etc.)?

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

21. Claims 24-32 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Furuta U.S. Patent 6,905,839 filed July 31, 2002.

For present claims 24, 25, 27, 28, 29, 30, 31, 32, and 37, Furuta teaches methods for determining in vivo cytochrome P450 3A activity (i.e. metabolism) of various compounds via isotope dilution mass spectrometry comprising producing labeled compounds and labeled internal standards, utilizing naturally occurring cytochrome P450 and naturally occurring reaction terminators, determining molecular ions (i.e. mass spectrometry; including most abundant), determining ratio, and determining amount of compound metabolized (please refer to the entire specification particularly abstract; columns 1-2, 4-11).

For present claim 26, Furuta teaches HPLC separation and gas chromatography (please refer to the entire specification particularly columns 9-10).

Therefore, the presently claimed method is anticipated by the teachings of Furuta.

Claim Rejections - 35 USC § 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. Claims 24-33 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Way et al. Journal of Analytical Toxicology 22: 374-382, 1998 (provided by applicants in the IDS) and Bertrand et al. European Journal of Pharmaceutical Sciences 11(suppl 2): S61-S72, 2000.

For present claims 24-33, Way et al. teach methods of analyzing secondary amines via isotope dilution gas chromatographic-mass spectrometry comprising providing tricyclic antidepressant drugs, producing stable derivatives of drugs with secondary amine groups, producing stable isotope internal standards including deuterium-labeled compounds, utilizing acid anhydride, extraction with organic solvent, HPLC, determining molecular ions, determining abundance, determining ion ratios, etc. (please refer to the entire specification particularly abstract; materials and methods; Figures 1-7; Tables I-III).

However, Way et al. does not teach determining metabolism of the drugs via cytochrome P450 enzymes.

For present claims 24 and 37, Bertrand et al. teach that high throughput screening of drugs for metabolism by cytochrome P450 is a standard technique in drug discovery including utilizing various mass spectrometry techniques (please refer to the entire specification particularly sections 3, 4.1.2-4.3.3).

All of the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods without changing the specific functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. For example, the P450 enzymes taught by Bertrand et al. could have been added into the method of analyzing amines via isotope dilution gas chromatographic-mass spectrometry taught by Way et al. to determine the metabolic rate of the amines.

24. Claims 24-33 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nguyen et al. U.S. Patent 5,908,927 issued June 1, 1999 and Bertrand et al. European Journal of Pharmaceutical Sciences 11(suppl 2): S61-S72, 2000.

For present claims 24-33 and 37, Nguyen et al. teach methods of determining the metabolism of codeine, morphine, heroin, and derivatives via gas chromatography mass spectrometry analysis comprising producing drug compounds, producing isotope labeled internal standards, HPLC, extraction, derivatization, quantitation, determination of molecular ion, determination of abundance (please refer to the entire specification particularly abstract; columns 1-5; Examples 1-9).

However, Nguyen et al. does not specifically teach cytochrome P450 enzyme metabolism.

For present claims 24 and 37, Bertrand et al. teach that high throughput screening of drugs for metabolism by cytochrome P450 is a standard technique in drug discovery including utilizing various mass spectrometry techniques (please refer to the entire specification particularly sections 3, 4.1.2-4.3.3).

All of the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods without changing the specific functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. For example, the P450 enzymes taught by Bertrand et al. could have been added into the method of analyzing metabolism of opiates via gas chromatography mass spectrometry taught by Nguyen et al. to determine the metabolic rate of the opiates in response to P450.

Conclusion

25. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Blair et al., 2002, Current Drug Metabolism, 3: 463-480 and Chu et al., 2000, Rapid Communications in Mass Spectrometry, 14: 207-214.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ADS
September 13, 2007

Mark L. Shibuya
MARK L. SHIBUYA
PRIMARY EXAMINER

O I P E IAP86
DEC 10 2007
PATENT & TRADEMARK OFFICE

December 5, 2007.

To : Examiner Amber Steele

Re: Application number 10/684,249. Art unit 1639

Dear Examiner Steele :

We, the applicants, sincerely admit our lack of knowledge in the prosecution of patent application. However we would like to continue to review the patent rules and show our best efforts to comprehend and comply with the rules. There are many "rejections" that we have to answer to the office:

1. Office Action :

Claims 34-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected species, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on July 16,2007.

Reply :

We acknowledge this action and ask to refer to office action number 6 for explanation.

2. Office Action :

The subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention. Applicant is required to furnish a drawing under 37 CFR 1.81(c). No new matter may be introduced in the required drawing. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d).

Reply :

We would like to submit drawings as mass spectra to facilitate the understanding of the invention. Each drawing is labeled on top as "New Sheet". A brief description of the drawings is added as a "new" section to describe the drawings. These drawings are mass spectra of derivatized chemical compounds of the example of the specification illustrating the combination of molecular ion and daughter ion of each derivatized compound as disclosed.

3. Office Action :

Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc. The abstract of the disclosure is objected to because the abstract contains legal phraseology (i.e. "said"). Correction is required. See MPEP 608.01(b).

Reply :

We ask to correct the "abstract of the invention" to comply with the above requirement. This part is labeled as "currently amended" and contains underlined added text and strikethrough delete text according to 37CFR1.121(b) (1).

4. Office Action :

Claims 24-33 and 37 are objected to because of the following informalities: An alternative preamble for claim 24 is suggested: "An automated method for determining metabolic stability of a library of compounds.. .". An alternative to method step h is suggested ". . .and the stable isotope labeled internal standard which corresponds to a compound of the library". In addition, library of compounds may be utilized when referring to more than one compound and compound may be utilized when referring to a single member of the library (please refer to claim 24 method steps a, d, g, 1; claims 27, 33). Claim 33 recites a Markush group. However, the proper format for a Markush claim is not utilized. Please refer to MPEP 5 803.02 which states that a Markush-type claim recites alternatives in a format such as "selected from the group consisting of A, B and C." See Ex parte Markush, 1925 C.D. 126 (Comm'r Pat. 1925). Applicants have written alternative language in the Markush group and not in the accepted form (i.e. "selected from a labeled acid anhydride or labeled acid chloride.. . .and labeled thiosocyanate").

The spacing of the lines of the claims is such as to make reading difficult. New application papers with lines 1 1/2 or double spaced on good quality paper are required. 37 CFR 1.52 (b) (2) (i); MPEP 608.01. Appropriate correction is required.

Reply :

We use the suggested preamble alternative for claim 24 to amend the claim. Other part of claim 24 are also amended accordingly. The Markush group of claim33 is no longer used. The amended specification will be submitted on good quality paper (24lbs wt) with double line spacing and with paragraph numbers.

5. Office Action :

Claims 24-33 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination.of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099- 1111, Friday January 5,2001. This is a written description rejection.

Claim 24 is drawn to a method for determining the metabolic stability of a library of compounds comprising (a) producing a stable isotope labeled internal standard via addition of a chemical reagent to a compound, (b) producing compounds that are identical in structure to the internal standards except for the stable isotope atoms, (c) separating the standards and compounds, (d) incubating compounds with cytochrome P450 enzyme systems, (e) adding quenching chemical reagents to terminate reactions, (f) adding internal Standards, (g) adding non-isotope labeled chemical reagents, (h) separating compounds form internal standards, (i) determining molecular ions, u) determining most abundant daughter ions, (k) determining ion rations, and (1) determining the percent remaining of each compound. The invention as claimed requires compounds, internal standards that correlate to the compounds, various chemical reagents including isotope labeled, non-isotope labeled, quenching, etc., and a member of the cytochrome P450 superfamily. The claimed invention does not include any structural information (i.e. actual structure or names of art-recognized species) regarding the compounds, internal standards, or chemical reagents except that the compound and internal standard must be identical in structure except for the stable isotope atoms of the internal standard. Therefore, the claimed invention includes all compounds, all internal standards with stable isotopes, and all chemical reagents without providing information regarding how the chemical reagents alter the structure of the compounds and internal standards.

The specification teaches a single example utilizing amines (i.e. amine 1, amine 2, amine 3, and amine 4) as compounds, acetamide-d3 internal standards, and chemical reagents including acetic anhydride-d6 (for producing internal standards), acetonitrile (tefminating reagent), sodium bicarbonate and acetic anhydride (for conversion). In addition, applicants also lists various generic compounds (i.e. drug compounds, amines, alcohols, aldehydes, and carboxylic acids), generic stable internal standards (i.e. drug compounds, amines, alcohols, aldehydes, and carboxylic acids with stable isotopes), the generic cytochrome P450 superfamily, and various chemical reagents (i.e. acid anhydride, acid chloride, chloroformate, isocyanate, thioisocyanate) without adequately describing how to utilize the various reagents in combination in the method as presently claimed or providing specific species of any of the claimed genera (i.e. compound, cytochrome P450 enzyme superfamily, etc.). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559,1571,39 USPQ2d 1895,1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species). Therefore, one skilled in the relevant art would not reasonably conclude that the applicants had possession of the invention as claimed.

See Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 , makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now* specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.). (See page 1117.) The

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amaen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

Reply :

We ask for permission to amend the specification to clarify the subject matter of our invention without introducing new matter according to 37CFR 1.121(b) (1). The necessary amendments will include addition of terms and example from cited literature, "rephrasing" of existing paragraphs by addition of new text to replace deleted text, addition of new paragraphs to replace deleted paragraphs, and addition of requested structural representations, all for the purpose of better description of the method of the invention.

The invention pertains to a method of quantitative analysis of library of chemical compounds by mass spectrometry (MS) analysis in a metabolic stability test. The subject matter as disclosed in the specification as method of synthesis of both labeled internal standards and "converted compounds" that are useful for the analysis of library compounds by mass spectrometry. The metabolic stability test becomes novel because of the synthesis, especially the automation capability of the synthesis method. We feel that it may be misleading to claim and disclose the subject matter as the novel metabolic stability test while the main focus of the invention is the synthesis. Therefore we ask for allowance to clarify the specification and the claims in such a way to direct the focus of the invention to methods of synthesis for the purpose of analysis by MS in a metabolic stability test without introducing new material but only reemphasizing materials already disclosed. The subject matter of the invention includes the one step simultaneous synthesis of labeled chemical compounds that can be used as labeled internal standards in the MS analysis of a library of chemical compounds in a metabolic stability test. The use of these labeled internal standards requires an additional reaction to be performed on the library compounds after their exposure to enzymes so that they can be effectively analyzed by MS. The subject matter of the invention also includes this additional one step simultaneous reaction.

A re-examination of cited references directs us to the use of a familiar term "derivatization" to describe the processes of our invention. This term refers to chemical reactions performed on samples in analytical analysis. "Derivatization" is a method that was found extensive application in gas chromatography mass spectrometry analysis of samples of biological origin. It is a method of chemically attachment of a chemical tagged group to the existing functional group of a chemical compound being analyzed in order to obtain better chromatographic and/or spectroscopic signal. Originally derivatization method focuses mainly on the preparation of less volatile chemical compounds for easy passage through the gas chromatography column, it is later found application in liquid chromatography mass spectrometry analysis for the purpose of producing better MS signal. We found the term "derivatization" useful in describing the method of our invention not only because derivatization method can produce better MS signal but it can open the way to synthesis of labeled chemicals not found in prior arts.

We ask for permission to introduce and define the terms “derivatization”, “derivatizing reagent”, “derivatized chemical compounds”, and “derivatized library compounds”to describe the synthesis of labeled internal standard and the additional reaction of our method in an effort to replace terms such as “converted compounds”, “labeled chemical reagent”, etc. We also ask to introduce and define the term “tagged chemical group” to clarify the intended function of the derivatization method in our invention.

The work of Jens Pietzsch et al. on the analysis of homocysteine by gas chromatography-mass spectrometry was cited as one of the references. We ask for permission to specifically describe the process of derivatization of homocysteine in this work to show that derivatization for MS analysis of homocysteine resulted in the chemical attachment of 3 tagged chemical groups for the purpose of obtaining better MS signal. Even though the derivatization of homocysteine transforms a thio-amino acid (homocysteine) to a thioester-acetamide acid ester (derivatized homocysteine), it is not the type of product that is significant to MS analysis, but rather it is the attachment of the 3 tagged chemical groups that results in an increase in the mass of homocysteine by the size of these groups. The same derivatization method when applied to a hydroxyl-amino acid such as tyrosine will transform it into an ester-acetamide acid ester product which is no longer a thioester, but which, upon MS analysis, produces ion signal also increased in mass by the size of 3 tagged chemical groups. So even though derivatization involves chemical reactions, its sole purpose is to obtain better signal upon instrumental analysis regardless of the type of compounds the chemicals turned out to be.

Permission is requested to amend the “background of the invention” as follows :

a) Paragraph [0001] is rephrased to emphasize the synthesis of labeled internal standards in the MS analysis of our invention.
b) Paragraph [0002] is rephrased to explain the metabolic stability test using Cytochrome P450 enzyme which was described in a deleted paragraph below.
c) Paragraph “With careful synthesis ....in the body” is deleted and its content is included in paragraph [0002].
d) Paragraph “Metabolic is ....said analysis” is deleted and its content is included in paragraph [0014].
e) Paragraph “Said MS method ....is performed” is deleted and its content is included in paragraph [0018].
f) Paragraph “Analysis of ....said extracts” is deleted and its content is included in paragraph [0003].
g) Paragraph “A mass spectrometric ....candidate compound” is deleted and its content is included in paragraph [0003].
h) Paragraph “The commonly used ....drug candidates” is deleted and its content is included in paragraphs [0003] and [0006].
i) Paragraph “Isotope dilution ....already added” is deleted and its content is included in paragraph [0005].
j) Paragraph “Using well known ....mass spectrometry” is deleted and its content is included in paragraph [0009].
k) Paragraph “Said efficient chemical ....for analysis” is deleted and its content is included in paragraph [0018].
l) Paragraph “This invention ....alkyl halide” is deleted and its content is included in paragraphs [0004], [0009], [0010], [0011], [0012], [0016].

m) Paragraph “Said efficient conversion ....MS analysis” is deleted and its content is included in paragraph [0005].

n) Paragraphs [0003], [0004], [0005], and [0006] are newly added paragraphs with no underlined text to replace the deleted paragraphs which have no underlined text but with bold start and end words. Paragraph [0005] specifically define terms “derivatization”, “derivatizing reagent”, “derivatized” chemical compound, “tag on”, “chemically attach”, “tagged chemical group” which form antecedent basis for the claims.

The “brief description of the invention” is also amended with added underlined text and strikethrough deleted text in double brackets to clarify the subject of the invention as a method of one step simultaneous synthesis of labeled chemical compounds that can be used as labeled internal standards. The method of the invention also includes a method of additional chemical reaction to be performed on the library compounds after enzyme reactions in a metabolic stability test as a condition for using the synthesized labeled chemical compounds as labeled internal standards.

Allowance is also requested for amendment of the “detailed description of the invention” to further clarify the synthesis method and the method of additional reaction. These 2 methods are further clarified by tables of derivatizing reagents, intended functional groups of library compounds, anticipated tagged chemical groups, and resulting derivatized products. These processes were described previously in the “background of the invention”. We feel that the description of these methods is more appropriately placed in the “detailed description of the invention”. Specifically the amendment of the “detailed description of the invention” is as follows :

a) Paragraph [0009] is amended with underlined added text and strikethrough deleted text in double brackets to further clarify subject matter of the invention as methods of one step simultaneous derivatization reactions for MS analysis purposes of a metabolic stability test. This paragraph also defines the limitation of library of chemical compounds to those containing at least one of the four functional groups.

b) Paragraph “Specifically ....thioisocyanates” and paragraph “Specifically ....isocyanates” are deleted with bold start and end words and are replaced by paragraph [0010] which is an added paragraph with no underlined added text. Paragraph [0010] combines contents of the 2 deleted paragraphs and contains structural representations of derivatizing reagents, functional groups, tagged chemical groups, and derivatized chemical compounds.

c) Paragraph [0011] is amended with underlined added text and strikethrough deleted text in double brackets to include structural representations of derivatizing reagents, functional groups, tagged chemical groups, and derivatized chemical compounds.

d) Paragraph [0012] is amended with underlined added text and strikethrough deleted text in double brackets to include structural representations of derivatizing reagents, functional groups, tagged chemical groups, and derivatized chemical compounds.

e) Paragraph “Specifically ....time intervals” is deleted with bold start and end words and its content is replaced by part of paragraph [0015].

f) Paragraph “Specifically …….solid phase extraction” is deleted with bold start and end words and is replaced by paragraph [0013] which is an added paragraph with no underlined added text.
g) Paragraph [0014] is amended with underlined added text and strikethrough deleted text in double brackets. This paragraph also contains information originally described in the deleted paragraph of the background of the invention.
h) Paragraph [0015] is amended with underlined added text and strikethrough deleted text in double brackets. This paragraph defines “stopped enzyme reaction”.
i) Paragraph [0016] is added to clarify the derivatization of the remainder of the library compounds as a condition for using the synthesized labeled internal standards. This paragraph contains contents of 2 deleted paragraphs originally in the background of the invention, namely paragraph “This invention…alkyl halide” and paragraph “Said efficient conversion….MS analysis”. This paragraph also includes structural representations of derivatizing reagents, functional groups, tagged chemical groups, and derivatized chemical compounds.
j) Paragraph [0017] is added to define a condition of derivatization of the remainder of library compounds, the 100% quantitative conversion This paragraph contains contents of a deleted paragraph originally in the background of the invention, namely paragraph “Said efficient conversion….MS analysis”.
k) Paragraph [0018] is amended with explanation of the experiment to show that the synthesis of labeled acetamides-d3 internal standards from acetic anhydride-d6 results in a mass increase of 45amu of the original 4 amines, and the additional reaction of library compounds with acetic anhydride results in a mass increase of 42amu of the original 4 amines. This paragraph contains information about the mode of MS analysis of a deleted paragraph originally in the background of the invention, namely paragraph “Said MS method…..performed”.
l) Paragraph [0019] is amended with structural representation of the acetamides and the acetamides-d3 to show that the combination of molecular ion and daughter ion are obtained from the mass spectrometry analysis of the derivatized chemical compound having that particular structural representation.
m) Paragraph [0020] is added to point out an advantage that the use of labeled derivatizing reagent in the synthesis of labeled internal standards not only results in chemical compounds having higher masses but also results in chemical compounds having desired enriched stable isotope atoms.

As requested, we ask for permission to amend the specification and the claims in such a way to include structural representation of chemicals and chemical groups. Structural representation of 4 functional groups common to members of library of chemical compounds are provided in text format as follows : amino groups represented as R_2NH , hydroxyl groups represented as ROH, carbonyl groups represented as R_2CO, carboxyl groups represented as RCOOH, wherein R is part of the library compounds composed of hydrogen, alkyl, aryl, hetero atom containing, cyclic, non-cyclic groups. Also provided are structural representation of labeled derivatizing reagents, labeled tagged chemical groups, and derivatized chemical compounds as follows :

Labeled deri. reagent	*Funct. group*	*Tagged group*	*Der. cpds*
$(R^*CO)_2O$	R_2NH , ROH	R*CO	R^*CONR_2 , R*COOR
R*COCl	R_2NH , ROH	R*CO	R^*CONR_2 , R*COOR
R*OCOCl	R_2NH , ROH	R*OCO	R^*OCONR_2 ,R*OCOOR
R*NCO	R_2NH , ROH	R*NHCO	$R^*NHCONR_2$,R*NHCOOR
R*NCS	R_2NH , ROH	R*NHCS	$R^*NHCSNR_2$,R*NHCSOR
R^*ONH_2	R_2CO	R*ON	R^*ONCR_2
R^*NHNH_2	R_2CO	R*NHN	R^*NHNCR_2
R*OH	RCOOH	R*	R*COOR
R*Cl	RCOOH	R*	R*COOR
R*Br	RCOOH	R*	R*COOR
R*I	RCOOH	R*	R*COOR

R* is CD_3 , $^{13}CD_3$, C_6D_5 , $^{13}C_6H_5$, $C_6D_5CH_2$, and $^{13}C_6H_5CH_2$

Structural representation of non labeled derivatizing reagents, tagged chemical groups, and derivatized library compounds are provided as follows :

Derivatizing reagent	*Funct. group*	*Tagged group*	*Der. cpds*
$(RCO)_2O$	R_2NH , ROH	RCO	$RCONR_2$, RCOOR
RCOCl	R_2NH , ROH	RCO	$RCONR_2$, RCOOR
ROCOCl	R_2NH , ROH	ROCO	$ROCONR_2$,ROCOOR
RNCO	R_2NH , ROH	RNHCO	$RNHCONR_2$,RNHCOOR
RNCS	R_2NH , ROH	RNHCS	$RNHCSNR_2$,RNHCSOR
$RONH_2$	R_2CO	RON	$RONCR_2$
$RNHNH_2$	R_2CO	RNHN	$RNHNCR_2$
ROH	RCOOH	R	RCOOR
RCl	RCOOH	R	RCOOR
RBr	RCOOH	R	RCOOR
RI	RCOOH	R	RCOOR

R is CH_3 , C_6H_5 , and $C_6H_5CH_2$

The above structural representation of the derivatized chemical compounds having the labeled tagged chemical group and the derivatized library compounds having the non labeled tagged chemical group illustrate how the tagged chemical groups chemically attached to the existing functional group. Allowance is also requested for providing structure representation of 4 acetamides and 4 acetamides-d3 whose mass spectral data are given as combinations of molecular ion and daughter ion in the example of the detailed description of the invention. These structural representations are added next to the names of the acetamides and the acetamides-d3 to specify that the ion combination is the result of mass spectrometric analysis of the particular derivatized chemical compound as follows:

Amine 1 : acetamide $C_6H_5CH_2CH(CH_3)NH(COCH_3)$: 178.1 → 91.0;
acetamide-d3 $C_6H_5CH_2CH(CH_3)NH(COCD_3)$: 181.2 → 91.0;

Amine 2 : acetamide $C_6H_5CH_2CH(CH_3)NH(CH_3)(COCH_3)$: 192.2 → 91.0;
acetamide-d3 $C_6H_5CH_2CH(CH_3)NH(CH_3)(COCD_3)$: 195.2 → 91.0;

Amine 3 : acetamide $(OCH_2O)C_6H_3CH_2CH(CH_3)NH(CH_3)(COCH_3)$: 236.2 → 105.0;
acetamide-d3 $(OCH_2O)C_6H_3CH_2CH(CH_3)NH(CH_3)(COCD_3)$: 239.3 → 105.0;

Amine 2 : acetamide $(OCH_2O)C_6H_3CH_2CH(CH_3)NH(CH_2CH_4)(COCH_3)$: 250.0 → 105.0;
acetamide-d3 $(OCH_2O)C_6H_3CH_2CH(CH_3)NH(CH_2CH_4)(COCD_3)$: 253.2 → 105.0;

The above structural representation of the acetamides-d3 and of the acetamides show the chemical attachment of the labeled tagged chemical group $COCD_3$ (acetyl-d3) and the tagged chemical group $COCH_3$ (acetyl) to the amino functional groups. It would further facilitate the connection of bond of the above tagged chemical groups to the amino functional group of the amines if allowance is granted for the inclusion of structural representations of the library of 4 amines in the example of the detailed description of the invention, paragraph [0018]. It would not be an introduction of new matter because if these amines were not used in the experiment, the combinations of molecular ions and daughter ions of acetamides-d3 and acetamides of these amines would not have been obtained as disclosed. Paragraph [0018] is also amended to include specific mass increase of 45amu and 42amu as a result of the chemical attachment of an acetyl-d3 tagged group and an acetyl tagged group. Paragraph [0020] is amended with structural representation of acetic anhydride-$^{13}C4$ and acetic anhydride-d6 and the corresponding labeled tagged acetyl group to point out the advantage of a one step introduction of carbon13 isotope.

6. Office Action :

Claims 34-36 are withdrawn from further consideration pursuant to 37 CFR

1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on July 16,2007.

Reply :

We acknowledge this action and ask for reconsideration of the restriction requirement for the following reason:

The subject matter of the invention as stated above is the synthesis of labeled internal standards and the additional reaction of the remainder of the library compounds for the MS analysis of a metabolic stability test. However the elected species is not the type of compounds (amine, ester, alcohol, etc.) resulting from the process of the invention. It is a compound with a mass increase as a result of the chemical attachment of the tagged chemical group that is crucial for MS analysis. So the elected species would be the "compound with a mass increase". As mentioned above, a specific example of derivatization of homocysteine in the work of Jens Pietzsch et al. demonstrates a mass increase by the chemical attachment of 3 tagged chemical groups to all 3 functional groups (amino, carboxyl, and thio groups) of homocysteine. The derivatization of the carboxyl group and the thio group occurs simultaneously with the derivatization of the amino group. The preparation of the carboxylic acid ethyl ester from the carboxyl function of homocysteine occurs simultaneously with the preparation of the acetamide from the amine function. In addition the preparation of the thioester from the thio group also happens simultaneously. The restriction of species based on the type of product resulted from the derivatization reaction is not appropriate because all 3 products are formed simultaneously. However if one regards the methods of our invention as methods of synthesizing compounds with mass increase due to the attachment of labeled tagged chemical group for MS analysis purposes, then the compounds with mass increase is regarded as one species. All the derivatized chemical compounds are obvious variants of the same species as far as MS analysis is concerned. We ask that the restriction of species be overuled and allow the consideration of claims 34,35, and 36. We have tried to make this point in earlier correspondence with the office by amending the claims but it is apparent that the point was not recognized by the office. We might have confused the office even more by submitting examples of chemical compounds not even disclosed in the specification in earlier correspondences.

7. Office Action :

Claims 24-33 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 recites the limitation "said stable isotope reagent", in line 4 of method step b. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "said non-isotope labeled converted compounds in lines 1-2 of method step c, line 3 of method step g, line 2 of method step I, line 2 of method step j. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "said terminated reactions" in lines 1-2 of method step f and in line 2 of method step g. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "said converted compound" in line 1 of method step h and line 1 of methods step k. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "said reactions" in lines 1-2 of method step h. There is insufficient antecedent basis for this limitation in the claim.

Claim 24 recites the limitation "said corresponding internal standard" in lines 1-2 of method step k. There is insufficient antecedent basis for this limitation in the claim.

Claim 27 recites the limitation "said sample" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the limitation "said internal standard" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 29 recites the limitation "said internal standard" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

Claim 29 recites the limitation "said chemical reagent" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

Claim 33 recites the limitation "said stable isotope reagent" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 33 recites the limitation "said resulting internal standards" in lines 4-5. There is insufficient antecedent basis for this limitation in the claim.

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention. The claims and the specification do not define the classes of library compounds. For example, does a class comprise a single compound, compounds that are structurally related, compounds that are functionally related, etc.? for failing to particularly point out and distinctly claim the subject matter which applicant

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite regards as the invention. One of skill in the art would not be able to determine the scope of the presently claimed invention. The claims and the specification do not define a 100% quantitative conversion. For example, is a 100% quantitative conversion a reaction wherein 100% of the reactants have formed a product, what are the parameters for quantification (i.e. mass, amount of final product, analysis of reactants, analysis of rate limiting reactant, etc.)?

Reply :

We ask for permission to amend the claims for compliance with the written description without introducing new matter according to 37CFR 1.121(b) (1) as follows :

Claim 24 is "rephrased" as

A method of one step simultaneous synthesis of labeled internal standards and additional one step chemical reaction for the purpose of determination of metabolic stability of a library of chemical compounds from the in vitro cytochrome P450 enzyme reactions by mass spectrometric (MS) analysis comprising the steps of :

a) synthesizing labeled internal standards of all library compounds simultaneously by a one step reaction of an authentic sample of all library compounds with a labeled derivatizing reagent having at least one enriched stable isotope atom to form derivatized chemical compounds having a mass increase by the chemical attachment of labeled tagged chemical group; and

b) isolating said labeled internal standards from said one step reaction by an aqueous extraction; and

c) contacting library compounds with cytochrome P450 enzymes in reactors at 37 degree Celcius for different time intervals; and

d) stopping enzyme reactions at different time intervals by addition of a solution containing an organic solvent and a known quantity of said labeled internal standards; and

e) contacting the remainder of said library compounds in stopped enzyme reactions with a non labeled version of said derivatizing reagent used in step a) to form derivatized library compounds having the same but non labeled tagged chemical groups as those of said labeled internal standards and wherein said labeled internal standards are not reacted with said non labeled derivatizing reagent; and

f) isolating said derivatized library compounds and said labeled internal standards from said stopped enzyme reactions by an aqueous extraction method; and

g) analyzing said derivatized library compounds and said labeled internal standards in said aqueous extract by mass spectrometry to determine the concentration of the remainder of said library compounds in stopped enzyme reactions and to calculate their remaining percentages.

The step "converting another portion……stable isotope reagent" is deleted to avoid misunderstanding of the subject matter. Also the steps of MS determination of molecular ions and daughter ions are deleted to avoid misunderstanding of the subject matter.

Claim 25 is canceled for the same above reason.

Claim 26 is amended to match the steps of amended claim 24.

Claim 27 is amended to define the limitation of said library of chemical compounds. Structural representation as disclosed in the specification are provided.

Claim 28 is amended to clarify the one step synthesis of labeled internal standards using a single labeled derivatizing reagent resulting in the chemical attachment of the same labebed tagged chemical group to all library compounds.

Claim 29 is amended by rephrasing for clarity purpose. Claim 29 emphasizes the requirement for using the synthesized labeled internal standards.

Claim 30 is amended to define a necessary reaction condition for both the synthesis of labeled internal standards and the additional reaction of derivatization of the remainder of library compounds.

Claim 31 is canceled because claim 25 is canceled and also because claim 24 already defines a chronological order of steps.

Claim 32 is amended to further define the limitation of organic solvent.

Claim 33 is amended to include the content of canceled claim 34. Structural representation of labeled derivatizing reagents, labeled tagged chemical group are included for clarity purpose. Also included is the information regarding the mass increase of the derivatized chemical compounds as a result of this reaction.

Claim34 is canceled because its content is included in claim 33.

Claim 35 is amended to include structural representation and mass increase information.

Claim 36 is amended to include structural representation and mass increase information.

Claim 37 remains unchanged and labeled as "original".

Claim 38 is amended to include the content of canceled claim 39. Structural representation of derivatizing reagents, tagged chemical group are included for clarity purpose. Also included is the information regarding the mass increase of the derivatized library compounds as a result of this reaction.

Claim 39 is canceled because its content is included in claim 38.

Claim 40 is amended to include structural representation and mass increase information.

Claim 41 is amended to include structural representation and mass increase information.

Claim 42 is added "new" to recite the limitation of enriched stable isotope atoms.

Claim 43 is added "new" to recite the limitation of the labeled derivatizing reagent used in the example.

Claim 44 is added "new" to recite the limitation of the derivatizing reagent used in the example.

8. Office Action :

Claims 24-33 and 37 are rejected under 35USC-112 as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Reply :

If the above amendments of specification and the claims are allowed, those skilled in the art can particularly point out the subject matter of the invention as methods of one step simultaneous synthesis of labeled internal standards and derivatization of library compounds for the MS analysis of a metabolic stability test. The objective of the invention is an improvement to the art of derivatization in MS analysis. This improvement is the use of labeled derivatizing reagent to attach a tagged chemical group containing enriched stable isotope atoms to a chemical compound in such a way that the derivatized product can be used as labeled internal standard for the MS analysis of that chemical compound. These methods of synthesis of labeled internal standard distinctly illustrates many advantages over the current method of synthesis of the labeled derivative of the chemical compound itself :

a) the method of this invention is a one step synthesis whereas the current synthesis of a labeled derivative of a chemical compound invariably requires multi step reactions.
b) The method of this invention is a simultaneous synthesis of more than one internal standard whereas the current synthesis of a labeled derivative of a chemical compound has to be carried out individually.
c) The method of this invention allows the feasible introduction of desirable stable isotope atoms such as carbon-13 (see paragraph [0020]) whereas the current synthesis of labeled derivative of a chemical compound relies on the availability of precursors that can be chemically reacted with carbon-13 reagents. There are cases where deuterium labeling can be performed by a process of hydrogen-

deuterium exchange. However, it is not known to date that carbon13 labeling can be performed by a process of carbon12-carbon13 exchange. Carbon13 labeling of organic chemicals for MS analysis is always a multi step synthesis.

d) Because the method of this invention is the synthesis of labeled chemical compounds by attachment of labeled tagged chemical group to existing functional group of chemical compounds, there are usually more than one choice of labeled internal standards. For example, the synthesized labeled methyl ester, labeled ethyl ester, etc. are different choices of labeled internal standard for the mass spectrometric analysis of a carboxylic acid.

e) A unique advantage of these methods of synthesis is the ability to carry out the synthesis of labeled internal standards by those who perform the analysis. Analytical chemists usually rely on organic chemists for the synthesis of labeled chemical compounds for MS analysis. The methods of this invention are both time saving and economical.

The combination of the one step synthesis of labeled internal standards and the one step derivatization of the library of chemical compounds for MS analysis distinctly claim the subject matter of the invention. This combination allows possible adaptation of the metabolic stability test to automated instruments, enable it a novel automated metabolic stability test.

9. Office Action :

Claims 24-33,36 and 37 are rejected under 35 USC-102 as being anticipated by Furuta U.S patent 6,905,839.

Reply :

Furuta teaches methods for determining in vivo cytochrome p450 enzyme activity by allowing human subjects to take labeled cortisol and analyzing their urine samples by MS for concentration of cortisol. The subject matter in his methods is the use of labeled cortisol for the in vivo enzyme test. It is noted that no derivatization method was claimed and no labeled derivatizing reagent was used for the synthesis of labeled cortisol. Our subject matter concerns the synthesis of labeled internal standards and the additional derivatization reaction in the MS analysis of library compounds to evaluate Cytochrome P450 enzyme activity in vitro. It is not anticipated from his methods that labeled internal standard (labeled cortisol) is prepared from cortisol by a one step derivatization.

10. Office Action :

Claims 24-33 and 37 are rejected under 35 USC-103(a) as being unpatentable (obviousness) over Way et al. Journal of Analytical toxicology 22:374-382, 1998 and Bertrand et al. European Journal of Pharmaceutical Sciences 11(suppl 2):S61-S72, 2000.

Reply :

Way et al teach methods of analysis of tricyclic antidepressant drugs having in common amino functional group by derivatization of the added deuterium labeled drugs with a non labeled derivatizing reagent (4-carbethoxyhexafluorobutyryl chloride) which also derivatized the tricyclic drugs in the sample at the same time. The requirement of these methods is the availability of deuterium labeled tricyclic drugs (imipramine-d4 and desipramine-d4) which must come from independent syntheses. It is noted that there were available only imipramine-d4 and desipramine-d4 but not labeled nortryptiline and amitryptiline for the MS analysis of imipramine, desipramine, nortryptiline, and amitryptiline. So even though a derivatizing reagent was used for the chemical attachment of a tagged chemical group to the common amino group of the tricyclic drugs, it is not anticipated from Way et al' methods that labeled nortriptiline and labeled amyitryptiline are synthesized by them using labeled derivatizing reagent. The methods of our invention, particularly the methods described in the example using derivatizing reagent acetic anhydride-d6 and acetic anhydride are suitable for the synthesis of labeled internal standards of the library of 4 above amine tricyclic drugs and the additional reaction to be performed on the sample of those amines for the MS analysis.

Bertrand et al teach method of high throughput screening of drugs for metabolism by Cytochrome P450 enzymes utilizing various MS techniques. It can be anticipated from methods of Way et al that derivatization of added labeled amines and the remainder of amine drugs in stopped enzyme reactions be carried out for the isotope dilution MS analysis. However it is not inferred or anticipated from the publication of Bertrand et al that a one step synthesis of labeled internal standards from a labeled derivatizing reagent and the drugs is a known art in high throughput cytochrome enzyme analysis.

11. Office Action :

Claims 24-33 and 37 are rejected under 35 USC-103 (a) as being unpatentable (obviousness) over Nguyen et al. U.S Patent 5,908,927 and Bertrand et al. European Journal of Pharmaceutical Sciences 11(suppl 2):S61-S72, 2000.

Reply :

Nguyen et al teach methods of determining the metabolism of opiates (codeine, morphine, heroin, and derivatives) via gas chromatography MS using labeled opiates as labeled internal standards. An independent synthesis of codeine-3-glucuronide-d3 is presented wherein the starting material for the synthesis is codeine-d3 which, in turn, is synthesized from codeine. An independent synthesis of morphine-3-glucuronide-d3 is also presented wherein the starting material is morphine-d3 which, in turn, is synthesized from morphine. The authors teach methods of determining the metabolism of drug compounds by MS analysis using labeled internal standards that are synthesized independently by multi-step syntheses. It is not anticipated from this work that labeled morphine-3-glucuronide and labeled codeine-3-glucuronide can be synthesized simultaneously by a one step derivatization of with a labeled derivatizing reagent.

From the works of Bertrand et al, Blair et al, and Chu et al, the evaluation of the extent of metabolism of drug compounds via cytochrome P450 enzyme reactions were made using various isotope dilution MS techniques which used labeled internal standards. It is anticipated that the methods of muti-step synthesis of labeled drug compounds as in the work of Nguyen et al.(US pat 5,908,927) are the methods to provide labeled internal standards for theses MS analyses. However, it is not anticipated from these works that a one step simultaneous reaction of drug compounds with a labeled derivatizing reagent is the method to make labeled internal standards as provided in our invention.

We made our best effort to comply with the rules of the patent office in amending the specification and the claims for the purpose of clarifying the subject matter of our invention. There may still be errors both in written requirement and in interpreting the patent rules. We ask for your continued advice and appreciate your past support and patience.

Sinverely and kind regards,

Nguyenduchoa

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